

REMARKS/ARGUMENTS

Claims 1 and 30 remain in the application. Claims 1 and 30 have been amended. Reconsideration of this application, as amended, is respectfully requested.

Claims 1 and 30 have been amended to specify that the bond between the reactive surface and the First Macromolecule is disrupted in a liquid medium to yield a conjugate soluble or dispersible in aqueous solution without disrupting the covalent bond existing between the First Macromolecule and the at least one Second Macromolecule. Support for this change can be found at Paragraph [0057] and at Paragraph [0110] of the specification. In Paragraph [0057], it is stated "... the production of the soluble or dispersible Macromolecular conjugate includes disrupting the stable bond between the solid-surface and the Macromolecule Conjugate in a liquid medium to yield a suspended or soluble Macromolecule Conjugate..." In Paragraph [0110], it is stated "...Release was effected by treatment with a dilute solution of hydroxylamine at room temperature, and was complete in 1 hour. Hydroxylamine reacts with the hydrazone linkage holding the protein assembly to the support, releasing the conjugate in its final form..."

Claims 1 and 30 stand rejected under 35 U. S. C. §103(a) as being unpatentable over Schwartz (U. S. 2003/0013857 A1). This rejection is respectfully traversed for the following reasons.

The present invention provides an improved method for conjugating macromolecules. See paragraph [0014]. The method comprises contacting a First Macromolecule to a reactive support to form a solid-bound macromolecular complex. If necessary, either or both steps of activating the First Macromolecule and deactivating the unreacted reactive moieties on the reactive surface are performed. A Second Macromolecule is activated, if necessary, and contacted to the First Macromolecule. After the solid, First Macromolecule, and Second Macromolecule bind to form a ternary complex, the bond between the solid and the First Macromolecule is disrupted to provide a macromolecular conjugate that is preferably soluble or dispersible in

aqueous solution. See paragraphs [0015], [0024], [0025], [0037], [0050], [0055], [0056], [0057].

One or more additional optional steps can be performed to add additional macromolecules and smaller molecules or atoms to the Macromolecular Conjugate. Any additional optional steps are preferably performed prior to disruption of the bond between the solid and the First Macromolecule. See paragraphs [0016], [0037].

Each step of the process, in fact the entire process, is preferably performed under aqueous conditions suitable to maintain the biological activity of an enzyme (e.g., bovine alkaline phosphatase). See paragraphs [0018], [0023].

Schwartz, U.S. Patent Application Publication No. 2003/0013857 A1 (hereinafter "Schwartz"), discloses modified solid supports that include solid supports that have been modified by reaction with a bifunctional reagent that possess a hydrazine or oxyamino group. These modified solid supports are useful in immobilization of biomolecules that possess or are modified to possess a carbonyl group. In one embodiment, aliphatic bifunctional hydrazide reagents are provided. These reagents include a cleavable bond for further manipulation. Cleavable bonds include, but are not limited to, acid cleavable, photocleavable and disulfide bonds.

Schwartz discloses a method of attaching a protein to a functionalized solid surface through a hydrazone linkage, wherein the protein is immobilized to a functionalized solid support via hydrazone bond formation. Schwartz discloses hydrazone bond formation as useful for conjugating biomolecules to other biomolecules and to fluorescent dyes. Schwartz discloses cleavage of the hydrazone bond to form useful products. Schwartz does not describe the preparation of conjugates comprising two macromolecules using conventional bifunctional reagents in paragraphs [0007] through [0016] or paragraph [0031]. Paragraphs [0007] through [0016] and [0031] of Schwartz refer to hydrazino, carbonyl, and oxyamino reagents.

None of the conjugates described in Examples 12, 14, 16, 20 of Schwartz correspond to the conjugates of the present invention, which comprise a First Macromolecule and at least one Second Macromolecule, because the conjugates described in Schwartz include a hydrazone bond,

which has been described as being cleavable, both by Schwartz and the specification of the present application. It is clear from paragraphs [0057] and [0110] of the specification of the present application that the linker between the First Macromolecule and the solid is cleavable while the linker between the First Macromolecule and the at least one Second Macromolecule is not cleavable. This conclusion is indisputable because if the bond between the First Macromolecule and the Second Macromolecule were cleavable, the conjugate would no longer exist after the First Macromolecule-Second Macromolecule complex is detached from the solid. Thus, it is clear that Schwartz teaches away from the method described herein because Schwartz calls for the cleavage of the First Macromolecule (protein) from the Second macromolecule (protein), which would destroy the conjugate. Moreover, both a cleavable linker and a non-cleavable linker are required in the method described herein, and Schwartz fails to disclose or suggest the use of a non-cleavable linker. In view of the foregoing, it is submitted that Schwartz does not render claims 1 and 30, as amended, obvious to one of ordinary skill in the art.

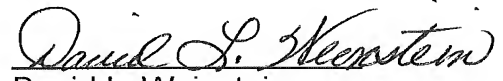
Upon a more detailed review of Schwartz, it can be seen that Schwartz describes methods for attaching a first macromolecule to a second macromolecule. See for example, paragraphs [0110], [0111], and [0112] of Schwartz. Schwartz also describes methods for attaching a chain of macromolecules to a surface. See, for example, paragraphs [0147], [0150], [0158], [0177], [0179], and EXAMPLES 6, 7, 8, 18, and 21 of Schwartz. However, Schwartz fails to disclose or suggest a multiple-step method that includes all of the steps of (1) linking a first macromolecules to a surface, (2) linking a second macromolecule to the first macromolecule, and (3) disrupting the link between the first macromolecule and the surface in order to free the conjugate comprising the first macromolecule and the second macromolecule from the surface without disrupting the covalent bond existing between the First Macromolecule and the at least one Second Macromolecule. Accordingly, Schwartz does not disclose or suggest a method containing all of the steps of the method described and claimed in this application. For this reason, it is submitted that Schwartz does not render claims 1 and 30, as amended, obvious to one of ordinary skill in the art.

In view of the foregoing, it is submitted that claims 1 and 30, as amended, are in condition for allowance, and official Notice of Allowance is respectfully requested.

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